

Michal Schwartz

T cell mediated neuroprotection is a physiological response to central nervous system insults

Received: 10 March 2000 / Accepted: 25 October 2000 / Published online: 22 December 2000
© Springer-Verlag 2000

Abstract The physiological conditions under which beneficial autoimmunity is evoked have never been documented. We recently demonstrated that autoimmune T cells directed against myelin-associated self-proteins, when passively transferred into rats or mice, reduce the spread of damage after traumatic injury to central nervous system axons. This finding raised a fundamental question: does this beneficial effect represent a physiological neuroprotective response that normally is too weak to be effective and requires boosting, or is it simply the welcome result of an *ex vivo* manipulation? It appears from our studies that trauma, at least in the central nervous system, evokes a stress signal that activates a T cell dependent response directed against self antigens, and that this response is physiological in nature, beneficial in intent, and amenable to boosting by active or passive immunization.

Keywords Beneficial autoimmunity · Central nervous system trauma · Neuroprotection

Abbreviations MBP: Myelin basic protein

An adaptive immune response, evoked by passive or active immunization, can benefit the injured central nervous system

Traumatic insult to the central nervous system causes degeneration of the directly injured neurons and usually also of neighboring neurons that escaped the primary injury but are affected by the toxicity of an extracellular environment rendered hostile as a consequence of the insult [1, 2, 3, 4, 5, 6, 7, 8]. Accumulated evidence from our laboratory shows that the traumatized CNS can benefit from active or passive immunization with myelin-

associated antigens [9, 10, 11, 12, 13, 14]. Thus, for example, in the severely injured optic nerve of the rat a significantly smaller number of initially spared neurons succumb to secondary degeneration if they are treated at the time of injury with T cells directed against myelin basic protein (MBP) than in untreated injured controls [9]. We have further shown that the effect of T cell treatment is long-lasting and is manifested both morphologically and functionally [11, 12]. More recently we have found that a similar effect, manifested in improved recovery of hind limb motor activity, is obtained by passive transfer of anti-MBP T cells into adult rats after contusive injury of the spinal cord, provided that the autoimmune T cell treatment is applied not later than 1 week after contusion [14]. Interestingly, although these injected T cells are capable of inducing the paralyzing disease experimental autoimmune encephalomyelitis, they do not interfere with the protective effect of the T cells or the favorable outcome of the spinal cord injury; at most, if administered 1 week after injury, they mask any early signs of apparent recovery and thus delay their onset [14]. The maximal recovery in rats treated with autoimmune T cells 1 week after contusion is similar to that seen in rats that had been treated immediately after the injury. A neuroprotective effect of the autoimmune T cells is also obtained by active immunization (vaccination) of the rats, before or immediately after the injury, with MBP emulsified in incomplete Freund's adjuvant [14]. Passive transfer of anti-MBP antibodies does not result in improved recovery, suggesting that the neuroprotective effect obtained by active immunization with MBP is mediated by T cells (E. Yoles et al., submitted). The protective autoimmunity was not necessarily accompanied by the development of autoimmune disease, as T cells directed against nonencephalitogenic cryptic epitopes of MBP show a similar beneficial effect [9].

This achievement of immune neuroprotection, whether by active or passive immunization, left some key questions unresolved: (a) Does immune neuroprotection represent a purely exogenous manipulation or does it reinforce a physiological response which in its spontaneous

M. Schwartz (✉)
Department of Neurobiology,
The Weizmann Institute of Science,
Rehovot, Israel
e-mail: michal.schwartz@weizmann.ac.il

form is too weak to be effective? (b) Is it possible to achieve the same neuroprotective effect using a safe (i.e., nonpathogenic) antigen? (c) What evokes the neuroprotective response to the T cells, and how is it mediated? These questions are addressed below.

Beneficial aut immunity is a physiological response

We have recently shown that traumatic injury to the rat spinal cord awakens a systemic neuroprotective response that mediates enhanced neuroprotection against subsequent injury to a second CNS site (E. Yoles et al., submitted). This beneficial effect is optimal when the time interval between the two lesions is 7–17 days. In addition, we have demonstrated a neuroprotective effect in newly injured rats injected with splenocytes obtained from the spinally injured rats. This latter finding strongly suggests (a) that protective autoimmunity is physiological, (b) that it is evoked by injury, and (c) that it is transferable by lymphocytes. It thus seems that traumatic CNS injury can evoke a beneficial endogenous autoimmunity, and not only a destructive endogenous autoimmunity, as has been claimed [15].

The concept that an injury-evoked neuroprotective response is mediated by T cells is further supported by our observation that the survival rate of retinal ganglion cells after optic nerve injury is significantly greater in transgenic mice overexpressing a T-cell receptor for MBP than in matched wild-type controls, but is less in transgenic mice overexpressing T cells to the non-self antigen ovalbumin (E. Yoles et al., submitted). It is also important to note that although activated anti-MBP T cells are known to cause experimental autoimmune encephalomyelitis, no disease develops in the transgenic mice used in this study. It is thus possible that while regulatory T cells in the transgenic mice suppress the destructive autoimmunity, they do not prevent expression of the protective autoimmunity. We further suggest that the neuroprotective and the destructive effects mediated by autoimmune T cells are regulated by a common mechanism (J. Kipnis et al., submitted). Moreover, using nude (athymic) mice, we recently found that the outcome of neuronal insult is worse in these mice than in matched wild-type controls (H. Schori et al., submitted), thus further supporting the notion that the endogenous neuroprotection evoked by CNS insult is T cell dependent.

Injury in the CNS is a stress signal that evokes an anti-self response

The concept that autoimmunity, once established, might be harmless or even useful, is not new [16, 17, 18, 19, 20, 21]. However, none of the theories put forward in this connection has described a situation in which the body calls for help from an autoimmune response. Even the danger signal model, which basically argues against discrimination between self and non-self in characteriz-

ing the signals triggering a beneficial immune response, views the response to self as a by-product of an adaptive immune response, a side effect that soon decays in the absence of a second signal to maintain it [16]. We suggest, on the basis of our results, that the autoimmune immune activity evoked in response to CNS trauma (E. Yoles et al., submitted; J. Kipnis et al., submitted; J. Schori et al., submitted) is a purposeful physiological event.

The adaptive immune response has generally been considered as an immune activity evoked by the organism to cope with stressful conditions caused by pathogens. Our observations suggest, however, that a stress signal transmitted from a traumatized tissue (in this case the CNS) to the immune system need not be pathogen related. This would imply that a response to self is not a quirk of nature, or an aberrant immune response, but rather a physiologically purposeful event.

Immunologists have traditionally viewed the functions of the adaptive immune response as neutralizing pathogens, preventing pathogen invasion of tissue, or counteracting the damage caused by pathogens that manage to invade. The damage caused by trauma, however, does not involve pathogens and thus has not been regarded by immunologists as posing the type of danger to the tissue that necessitates an adaptive immune response. Opinions differ as to the mechanisms by which self becomes invisible to the immune system, for example, by clonal deletion, anergy, or tolerance [16, 17, 18, 19, 20, 21]. If trauma can indeed act as a stress signal that activates a helpful immune response, a number of questions arise. Does this occur in all tissues? If not, why not? Since the role of the immune system is tissue protection, defense, and maintenance, does this signal always operate for the organism's benefit? How is it related to autoimmune disease? Does the trauma-related stress signal vary from tissue to tissue? It is possible that what determines whether a beneficial autoimmune response is evoked in a particular tissue depends on the severity of the threat. Trauma in the CNS potentially poses more of a threat to the individual than trauma in other tissues because of the self-perpetuating spread of degeneration [1, 2, 3, 4, 5, 6, 7, 8, 22] and the fact that terminally damaged neurons are irreplaceable. The stress signal elicited by trauma in the CNS can therefore be expected to be more profound. For example, the traumatized CNS might transmit – in addition to the signal sent by the damage itself – a second, as yet unidentified, distress signal, thereby converting T cells into effector helper cells with trauma-related activity. This implies that in traumatically injured non-CNS tissues that do not evoke an autoimmune response (beneficial or otherwise) the second signal is insufficient to activate T cells and/or to maintain them in an active form that enables them to become effectors. The specificity of the evoked T cells (in terms of the self-epitopes that activate them and are recognized by them) might, even in the CNS, vary according to the site of injury. It is conceivable that trauma-related distress signals activate T cells of other relevant

self-epitopes for protective purposes. It is also possible that in some individuals, because of their genetic make-up, an injury-induced beneficial autoimmune response cannot be expressed (J. Kipnis et al., submitted).

How does the response evoked in the protective autoimmune T cells exert its effect on the damaged tissue? It is possible that the active molecules produced by the effector helper T cells after trauma-associated damage are neurotrophins [12, 23, 24]. It also seems reasonable to assume that their secretion by the effector (autoimmune) T cells is antigen dependent [12]. An alternative possibility is that the T cells involved in autoimmune protection acquire a novel phenotype, which we have tentatively designated Th-NP, i.e., helper T cells with a propensity for neuroprotection (O. Butovsky et al., submitted).

Active immunization for neuroprotection with a safe peptide

If the observed immunological neuroprotection is to be exploited for clinical purposes, it will obviously be necessary to find ways immunize with "safe" CNS antigens, or with antigens that cross-react with self antigens but are themselves nonpathogenic. We have found that active immunization of rats or mice with a nonpathogenic cryptic epitope derived from myelin oligodendrocyte glycoprotein, a myelin protein, is as effective as MBP in protecting damaged optic axons by slowing down the death of their cell bodies [25]. Because individuals differ in their repertoires of MHC class II antigens, however, it is not possible to define a universally "safe" sequence in potentially pathogenic myelin-associated proteins for clinical use.

In exploring ways to achieve neuroprotection by vaccination we have examined the therapeutic efficacy of a synthetic polymer, copolymer-1, which can cross-react with T cells specific to myelin proteins, and is in clinical use as a drug for patients with multiple sclerosis [26]. Thus, its safety in terms of pathogenicity has already been established. To our surprise and satisfaction, active immunization with this drug, or passive transfer of the autoimmune T cells with which it cross-reacts, led to significant neuroprotection, manifested by significant reduction in secondary degeneration, after optic nerve injury in rats or mice [27].

Implications

Taken together, the results of our studies further imply that autoimmune protection, being the body's own physiological (although inadequate) response to injury, is worth augmenting for therapeutic purposes [28, 29]. Such a therapeutic approach, which until now has been neglected and even shunned by immunologists, might represent a therapeutic gold mine. Its exploration can also be expected to unravel some long-standing enigmas, including the meaning of a danger signal in immunology

and the way in which the immune response is evoked. It is clear from our studies that the question is not whether autoimmunity is produced, or how self is distinguished from non-self, but how to control the immune response to self so as to derive the maximum benefit with minimum threat.

Acknowledgements Michal Schwartz holds The Maurice and Ilse Katz Professorial Chair in Neuroimmunology. The author thanks Shirley Smith for editing the manuscript.

References

- Yoles E, Schwartz M (1998) Degeneration of spared axons following partial white matter lesion: implications for optic nerve neuropathies. *Exp Neurol* 153:1-7
- Lu J, Ashwell KW, Waite P (2000) Advances in secondary spinal cord injury: role of apoptosis. *Spine* 25:1859-1866
- Guth L, Zhang Z, Steward O (1999) The unique histopathological responses of the injured spinal cord. Implications for neuroprotective therapy. *Ann NY Acad Sci* 890:366-384
- Faden AI (1993) Experimental neurobiology of central nervous system trauma. *Crit Rev Neurobiol* 7:175-186
- Ransom BR, Stys PK, Waxman SG (1990) The pathophysiology of anoxic injury in central nervous system white matter. *Stroke* 21:52-57
- Agrawal SK, Fehlings MG (1996) Mechanisms of secondary injury to spinal cord axons in vitro: role of Na^+ , $\text{Na}^{(+)}\text{-K}^{(+)}\text{-ATPase}$, the $\text{Na}^{(+)}\text{-H}^{+}$ exchanger, and the $\text{Na}^{(+)}\text{-Ca}^{2+}$ exchanger. *J Neurosci* 16:545-552
- Hovda DA, Yoshino A, Kawamata T, Katayama Y, Becker DP (1991) Diffuse prolonged depression of cerebral oxidative metabolism following concussive brain injury in the rat: a cytochrome oxidase histochemistry study. *Brain Res* 567:1-10
- Lynch DR, Dawson TM (1994) Secondary mechanisms in neuronal trauma. *Curr Opin Neurol* 7:510-516
- Moalem G, Leibowitz-Amit R, Yoles E, Mor F, Cohen IR, Schwartz M (1999) Autoimmune T cells protect neurons from secondary degeneration after central nervous system axotomy. *Nat Med* 5:49-55
- Moalem G, Monsonego A, Shani Y, Cohen IR, Schwartz M (1999) Differential T cell response in central and peripheral nerve injury: connection with immune privilege. *FASEB J* 13:1207-1217
- Moalem G, Yoles E, Leibowitz-Amit R, Muller-Gilgor S, Mor F, Cohen IR, Schwartz M (2000) Autoimmune T cells retard the loss of function in injured rat optic nerves. *J Neuroimmunol* 106:189-197
- Moalem G, Gdalyahu A, Shani Y, Otten U, Lazarovici P, Cohen IR, Schwartz M (2000) Production of neurotrophins by activated T cells: implications for neuroprotective autoimmunity. *J Autoimmunol* (in press)
- Hauben E, Nevo U, Yoles E, Moalem, Agranov E, Mor F, Akselrod S, Neeman M, Cohen IR, Schwartz M (2000) Autoimmune T cells as potential neuroprotective therapy for spinal cord injury. *Lancet* 355:286-287
- Hauben E, Butovsky O, Nevo U, Yoles E, Moalem G, Agranov E, Mor F, Leibowitz-Amit R, Pevsner S, Akselrod S, Neeman M, Cohen IR, Schwartz M (2000) Passive or active immunization with myelin basic protein promotes recovery from spinal cord contusion. *J Neurosci* 20:6421-6430
- Popovich PG, Stokes BT, Whitacre CC (1996) Concept of autoimmunity following spinal cord injury: possible roles for T lymphocytes in the traumatized central nervous system. *J Neurosci Res* 45:349-363
- Matzinger P (1994) Tolerance, danger, and the extended family. *Annu Rev Immunol* 12:991-1045
- Cohen IR (1988) The self, the world and autoimmunity. *Sci Am* 258:52-60

18. Jerne NK (1984) Idiotypic networks and other preconceived ideas. *Immunol Rev* 79:5–24
19. Janeway CA Jr (1992) The immune system evolved to discriminate infectious nonself from noninfectious self. *Immunol Today* 13:11–16
20. Jameson SC, Hogquist KA, Bevan MJ (1995) Positive selection of thymocytes. *Annu Rev Immunol* 13:93–126
21. Bretscher P, Cohn M (1970) A theory of self-nonself discrimination. *Science* 169:1042–1049
22. Povlishock JT, Jenkins LW (1995) Are the pathobiological changes evoked by traumatic brain injury immediate and irreversible? *Brain Pathol* 5:415–426
23. Wekerle H, Bradl M, Linington C, Kaab G, Kojima K (1996) The shaping of the brain-specific T lymphocyte repertoire in the thymus. *Immunol Rev* 149:231–243
24. Kerschensteiner M, Gallmeier E, Behrens L, Leal VV, Misgeld T, Klinkert WE, Kolbeck R, Hoppe E, Oropeza-Wekerle RL, Bartke I, Stadelmann C, Lassmann H, Wekerle H, Hohlfeld R (1999) Activated human T cells, B cells, and monocytes produce brain-derived neurotrophic factor in vitro and in inflammatory brain lesions: a neuroprotective role of inflammation? *J Exp Med* 189:865–870
25. Fisher J, Yoles E, Levkovitch-Verbin H, Kay JF, Ben-Nun A, Schwartz M (2000) Vaccination for neuroprotection in the mouse optic nerve: implications for optic neuropathies. *J Neurosci* (in press)
26. Teitelbaum D, Arnon R, Sela M (1997) Copolymer 1: from basic research to clinical application. *Cell Mol Life Sci* 53:24–28
27. Kipnis J, Yoles E, Porat Z, Mor F, Sela M, Cohen IR, Schwartz M (2000) T cell immunity to Copolymer-1 confers neuroprotection on the damaged optic nerve: possible therapy for optic neuropathies. *Proc Natl Acad Sci USA* 97:7446–7451
28. Schwartz M, Moalem G, Leibowitz-Amit R, Cohen IR (1999) Innate and adaptive immune responses can be beneficial for CNS repair. *Trends Neurosci* 22:295–299
29. Schwartz M, Cohen IR, Lazarov-Spiegler O, Moalem G, Yoles E (1999) The remedy may lie in ourselves: prospects for immune cell therapy in central nervous system protection and repair. *J Mol Med* 77:713–717